Remarks

Status of the Claims

Claims 8-10, 33-34, 39, 42-91, 96-98, 100, and 102-105 were cancelled with the amendment filed on October 17, 2003. Claims 1-6, 11-30, 92-93, 99, 106-114, and 123 are cancelled with this amendment. Claims 125-137 are new. Accordingly, claims 7, 31-32, 35-38, 40-41, 94-95, 101, 115-122, and 124-137 are pending. Support for the new claims is detailed below. No new matter has been added by this amendment.

The species elected for examination in Amendment A of April 2002 is the species of Example 1 on page 157 of the specification. This is the species having a thienyl in the A position. The currently pending claims which read on this species are claims 7, 31-32, 35-38, 40-41, 94-95, 101, 115-122, and 124-131.

The currently pending claims which do not read on this species are claims 132-137. However, these claims are within the scope of claim 7 in that they are compounds in which A is group consisting of pyrazolyl (claim 132, 136), isoxazolyl (133, 134), pyridinyl (135), or furanone (137). According to MPEP § 809.02(e), whenever a generic claim (claim 7) is found to be allowable in substance, action on the species claims shall thereupon be given as if the generic claim were allowed. Thus, if it is determined that the elected species is patentable, it is incumbent upon the Office to search additional species that fall within any allowable generic claims.

Support for new claims 125-137

Support for claim 125 can be found, e.g., on page 10, lines 15-16, and page 11, lines 1-7.

Support for claim 126 can be found, e.g., on page 10, lines 18-21, and page 11, lines 20-24.

Support for claim 127 can be found, e.g., on page 10, lines 15-18, and page 11, lines 24-26.

Support for claim 128 can be found, e.g., on page 10, lines 15-18.

Support for claim 129 can be found, e.g., on page 12, lines 11-31, and page 13, lines 1-3.

Support for claims 130 and 131 can be found, e.g., on page 118, lines 28-31, and page 119, line 1.

Support for claims 132-137 can be found in specific examples and in general definitions of compounds of Formula I. Specifically, compound of claim 132 is shown on page 34, and has R2 as amino, A as pyrazolyl, R1 as phenyl substituted with C_{1-2}-alkyl, and R3 as C_{1-3}-haloalkyl.

The compound of claim 133 is shown on page 69, and has R2 as amino, A as isoxazolyl, R1 as phenyl, R3 as C_{1-2}-alkyl.

The compound of claim 134 is shown on page 69, and has R2 as propionyl substituted amine group, A as isoxazolyl, R1 as phenyl, and R3 as C_{1-2}-alkyl. It is stated in the specification that R2 is selected from methyl and amino groups. Applicants note that the compound described in claim 134 is a prodrug, and that it is established that the propionyl substituted amine group is metabolized to the

amino group in the body. Prodrugs are discussed, e.g., on pages 116-118.

The compound of claim 135 is shown on page 89, and has R2 as methyl, A as pyridinyl, R1 as pyridinyl substituted with C_{1-2}-alkyl, and R3 as halo.

The compound of claim 136 is shown on page 34, and has R2 as amino, A as pyrazolyl, R1 as phenyl substituted with C_{1-2}-alkyl and C_{1-2}-alkoxy group, and R3 as C_{1-2}-haloalkyl. Compound of claim 137 is shown on page 76, and has R2 as methyl, A as furanone, R1 as phenyl, and R3 as oxy group.

Preparation of compounds of claims 132, 134, and 137 are shown in Examples 4, 23, and 24, respectively.

Rejection Pursuant to 35 U.S.C. § 112, First Paragraph

Claims 1-8, 11-16, 31-32, 35-38, 40, 41, 92, 94, 99, 101, and 105-113 were rejected under §112, first paragraph for lack of enablement. In view of the above amendment, the rejection of claims 1-6, 8, 11-16, 92, 99, and 105-113, which have been cancelled, is moot.

Reconsideration is requested of the rejection of claims 7, 31-32, 35-38, 40, 41, 94 and 101 under §112, first paragraph.

Claim 7

The basis for the rejection is the assertion on page 2 of the Office action that the specification does not provide enablement "for the radicals A equal to all 5 or 6 membered partially saturated or unsaturated heterocyclic rings, R3 equal to heterocyclyl, heterocycloxy, or

heterocyclyl C1-3 alkyl rings." Applicants have now cancelled the claims of this scope. The broadest claims now pending are of the breadth of claim 7, wherein A is a radical selected from the group consisting of a) thienyl, b) furanone, c) oxazolyl, d) pyrazolyl, e) cyclopentenyl, and f) pyridinyl. The Office acknowledges on page 3 of the Office action that the compound is enabled for radicals b) furanone, c) oxaxolyl, d) pyrzolyl, and f) pyrydinyl:

> Applicant has not enabled preparation and use of derivatives to support the breadth of claims which includes radicals A and R3 of the compound of formula 5-6 membered partially saturated or unsaturated heterocyclic rings, heterocycloxy, or heterocyclyl C1-3 alkyl rings **other than** imidazole, oxazolone, isooxazole, furanyl, pyrazole, pyridinyl, or oxazole. (emphasis added).

With regard to the compound where the substituent A is radical (a) (thienyl) from the above list, Schemes V-VII beginning at page 128 describe preparation of intermediates useful in the preparation of the thiophene-containing compounds, and Schemes VIII-XI describe the preparation of the thiophene-containing compounds themselves. Examples 1 and 2 beginning at page 157 detail the preparation and characterization of the following thiophene-containing compounds:

2-fluoro-4-(4-phenyl-3-thienyl)benzenesulfonamide; and
3-[3-fluoro-4-(methylsulfonyl)phenyl]-4-phenylthiophene.

Furthermore, the general structure of thiophene-containing compounds and approximately 90 exemplary compounds are listed on pages 35-39, including, for example:

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;

3-(3,4-dichlorophenyl)4-[3-fluoro-4-(methylsufonyl)phenyl thiophene;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;

2-fluoro-4-[4-(3,5-dimethylphenyl)-3-thiophenyl] benzenesulfonamide; and

2-fluoro-4-[4-cyclopentyl-3-thiophenyl] benzenesulfonamide.

With regard to compounds encompassed by claim 7 wherein A is sutstituent(e) cyclopentene, cyclopentene-containing compounds are described on pages 76-81, and also include general formulas and approximately 95 exemplary compounds. Some of the exemplary compounds include:

2-fluoro-4-[2-(3,4-dimethylphenyl)cyclopenten-1-yl) benzenesulfonamide;

4-[2-(3-chlorophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone;

4-[2-(3-methyl-4-bromophenyl)cyclopenten-1-yl]-2-fluorophenyl methyl sulfone; and

4-[2-cyclohexylcyclopenten-1-yl]-2-fluorophenyl methyl sulfone.

Furthermore, methods for preparing compounds of claim 7, which contain cyclopentene as radical A are described, e.g., in Scheme XXXII in the specification.

With respect to the R_3 position in compounds of Formula I, Schemes I-XXXVI beginning on page 124 of the specification and the working examples describe methods for

preparing compounds with a large number of differing R_3 substituents.

The standard for enablement is whether one of ordinary skill in the art could make or use the claimed invention from the disclosures in the application coupled with information generally available to those skilled in the art without undue experimentation. The mere fact that some experimentation may be necessary to select and prepare compounds having a substituent not named in the specification does not render the specification non-enabling. As stated by the Board of Patent Appeals:

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art . . . The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.[1]

Furthermore, as noted above, patent applicants are not required to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general knowledge of the art would enable one of ordinary skill in the art to make and use the invention.

In the Wands case cited in the Office action, the claim at issue required using an antibody "wherein said

[1] Ex parte Forman, 230 U.S.P.Q. 546, 547 (BPAI 1986); see also MPEP 2164.06.

antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9M^{-1}." 8 USPQ2d p. 1402. The Federal Circuit discussed several of the relevant factors and concluded that "undue experimentation would not be required to practice the invention." 8 USPQ2d 1406.

With regard to the factor of "the amount of direction provided by the inventor," the Federal Circuit concluded that Wands provided "significant guidance and direction on how to practice the invention and present[ed] working examples." The Wands patent (4,879,219) is 18 columns long, including two columns of claims. Applicants' present specification is 196 pages long prior to the claims, including 75 pages (121-196) devoted to synthesis, working examples, and screening. The present specification provides over thirty synthetic schemes for the preparation of the fluoro-substituted benzenesulfonamides of Formula I generally, as well as for the preparation of particular classes of compounds within the scope of Formula I having a diverse range of heterocyclic groups for A, in addition to intermediates useful in their preparation. The specification lists twenty-four examples illustrating the preparation of particular species within the scope of Formula I. The specification reports references describing related compounds having a multitude of heterocyclic ring groups (including oxazolyl, oxazolonyl, pyrrolyl, pyrazolyl, imidazolyl, furanonyl, isoxazolyl, pyrazolyl, thiophenyl, furyl, pyridinyl, thiazolyl, imidazolyl, benzimidazolyl, indanonyl, benz[g]indazolyl, benzopyranyl,

benzopyranopyrazolyl, and heteroarylpyranopyrazolyls). One skilled in the art, equipped with the detailed disclosure of the instant specification, and familiar with basic synthetic organic chemistry, could readily adapt the synthetic schemes and examples described in the specification to prepare compounds within the scope of Formula I, having different heterocyclic groups for A than those specifically described in the schemes. Such adaptation is clearly within the abilities of one skilled in the art, and while some experimentation may be needed, such experimentation could be routinely performed by the skilled artisan, i.e., the adaptation could be accomplished without undue experimentation.

With regard to "the level of skill," the Federal Circuit stated "There was a high level of skill in the art at the time when the application was filed." 8 USPQ2d 1406. In the present situation, the level of skill of pharmaceutical chemists in the field of chemical synthesis is similarly high.

With regard to "the nature of the invention," the Federal Circuit in Wands stated that

> "the nature of monoclonal antibody technology is that it involves screening hybridomas to determine which ones secrete antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody."

Similarly in the present case, the nature of the invention requires reasonable screening, and pharmaceutical chemists in the field of chemical synthesis are prepared to screen compounds falling within the claim scope.

With regard to "working examples," Wands conducted just ten fusion experiments to produce hybridomas having the required binding affinity (8 USPQ2d 1405), and carried out the entire synthesis and screening procedure just three times. 8 USPQ2d 1407. The present specification provides 24 detailed working examples of syntheses and 24 sets of "Biological Evaluation" (p.192). This cannot fairly be deemed to favor a finding of non-enablement.

With regard to "state of the art," the state of the art is especially well developed in the fields of chemical synthesis and screening for pharmaceutical activity.

With regard to the "breadth of the claims," the Federal Circuit noted that of 143 candidate antibodies produced by Wands, his testing of just nine and proving the required activity of just four (8 USPQ2d 1405), not even considering countless others which Wands did not make, was sufficient to support claims of the following breadth: "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^9 M^{-1}$." This breadth, deemed acceptable, is much broader than a claim limited to those antibodies Wands produced or tested. Against this background, applicants respectfully submit that the breadth of their claims is reasonable in light of the 196 pages of explanatory specification including 75 pages devoted to synthesis, working examples, and screening.

With regard to the "level of predictability," the Federal Circuit in Wands noted that viewing the data as proposed by the Board, only four of 143 of Wands'

hybridomas, or 2.8% of those produced (not even considering those not produced), were proven to have the activity required by the claims. 8USPQ2d 1405. In the present specification many more than candidates than four were tested (24; see Biological Evaluation, p. 192 ff.), and screening according to the procedures well documented in the specification is well within the ordinary skill in the art.

With regard to the "quantity of experimentation," in Wands nine of 143 hybridomas were tested, and four were determined to have the required activity. This left 130+ hybridomas produced untested, as well as countless others not even produced. The present applicants should similarly not be precluded from patent protection on the basis they have left a considerable quantity of compounds untested, because, as stated by the Board:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.[2]

Patent applicants are not required to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general

[2] Ex parte Forman, 230 U.S.P.Q. 546, 547 (BPAI 1986); see also MPEP 2164.06.

knowledge of the art would enable one of ordinary skill in the art to make and use the invention.[3]

In view of the above, applicants submit that compounds of claim 7, including thienyl- and cyclopentene-containing compounds, are enabled and respectfully request withdrawal of the enablement rejection of claim 7.

Claim 31 and Dependent Claims 32-38 and 40-41

Claim 31 relates to compounds of Formula III which specifically require a thiophene group rather than the broader radical A of claim 7. Accordingly, compounds of Formula III (claim 31) are a subgroup of compounds of Formula I (claim 7).

Schemes V-VII beginning at page 128 describe preparation of intermediates useful in the preparation of the thiophene-containing compounds, and Schemes VIII-XI describe the preparation of the thiophene-containing compounds themselves. Examples 1 and 2 beginning at page 157 detail the preparation and characterization of the following thiophene-containing compounds:

2-fluoro-4-(4-phenyl-3-thienyl)benzenesulfonamide; and
3-[3-fluoro-4-(methylsulfonyl)phenyl]-4-phenylthiophene.

Furthermore, the general structure of thiophene-containing compounds and approximately 90 exemplary compounds are listed on pages 35-39, including, for example:

[3] In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970).

3-phenyl-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;

3-(3-bromophenyl)-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;

3-(3,4-dichlorophenyl)4-[3-fluoro-4-(methylsufonyl)phenyl thiophene;

3-cyclohexyl-4-[3-fluoro-4-(methylsulfonyl)phenyl] thiophene;

2-fluoro-4-[4-(3,5-dimethylphenyl)-3-thiophenyl] benzenesulfonamide; and

2-fluoro-4-[4-cyclopentyl-3-thiophenyl] benzenesulfonamide.

Applicants therefore respectfully submit that claim 31 is enabled and request its allowance. Furthermore, claims 32-38 and 40-41 depend from claim 31, and are enabled for the same reasons as claim 31.

Claims 94 and 95

Claim 94 and 95 are directed to pharmaceutical compositions comprising a therapeutically-effective amount of a compound of claim 31 or claim 7, respectively. These pharmaceutical compositions and methods of preparing such pharmaceutical compositions in forms, such as, e.g., capsules, tablets, and topical ointments, are described in detail in the specification. See, for example, page 118, line 24 through page 121, line 23. Accordingly, applicants submit that claims 94 and 95 are enabled.

Claim 101 and 115-121

Claim 101, which is directed to a method of treating inflammation comprising administering a therapeutically-effective amount of a compound of Formula III (defined as

above for claim 31), is enabled by the synthetic schemes noted above (i.e., Schemes VIII-XI, which describe the preparation of compounds of Formula III); moreover, the specification describes compounds of Formula III as COX-2 inhibitors and provides experimental data showing their efficacy as such. See, e.g., Table I and II, specifically the entries for Examples 1 and 2. These entries show that the compounds of Formula I are efficacious at selectively inhibiting COX-2, thereby mediating the method of treatment of claim 101.

Accordingly, applicants submit that claim 101 is enabled. Claims 115-121 depend from claim 101, and are enabled for the same reasons as claim 101.

Claim 124

Claim 124 is analogous to claim 7 in scope with regard to the A substituent in that it is directed to a method of treating inflammation comprising administering a therapeutically-effective amount of a compound of Formula I with the express requirement that A be a substituent selected from the group consisting of thienyl, furanone, isoxazolyl, pyrazolyl, cyclopentenyl and pyridinyl. The specification describes these methods in detail. See, e.g., pages 10-14, where a number of inflammation-related disorders that may be treated with compounds of Formula I are listed. These disorders include, e.g., arthritis, asthma, psoriasis, retinitis, and benign and malignant tumors. The specification further provides *in vitro* data regarding the COX-1 and COX-2 activities of these

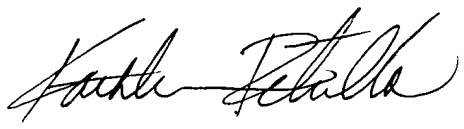
compounds. See, e.g., Table 1 and 2, which provide data about selective COX-2 inhibition of compounds of Formula I. In light of this disclosure, and for the reasons given above with respect to claims 7 and 101, claim 124 is enabled by the specification. Claims 125-131, added with this amendment, depend from claim 124.

Conclusion

In light of the foregoing remarks, it is respectfully submitted that the pending claims satisfy the requirements of §112, first paragraph. Favorable reconsideration and early allowance of all claims are respectfully requested.

Applicants request an extension of time to and including May 24, 2004 for filing a response to the above-mentioned Office action. A check in the amount of $110.00 in payment of the applicable extension fee is enclosed. The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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